DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/16/2009 has been entered.

Status of Claims

Claim 13 has been amended. Claims 13-15, 18-22 are pending, of which claims 18 and 21 have been withdrawn by Applicant. Claims 13-15, 19, 20 and 22 are examined herein on the merits for patentability.

Response to Arguments

Any rejection not reiterated herein has been withdrawn as being overcome by amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

> art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14 and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a method as claimed in claim 13, wherein the contrast agent comprises a contrast agent substrate, wherein the target is abnormally expressed enzyme, such that the contrast agent changes pharmacodynamic properties and/or pharmacokinetic properties upon a chemical modification from a contrast agent substrate agent to a contrast agent product upon a specific enzymatic transformation. However, claim 13, from which claims 14 and 15 depend, defines that the target is the estrogen receptor in line 7 of the claim. The specification as originally filed does not describe that the estrogen receptor is an enzyme. See published paragraphs 0016-0018, which describes that target receptors include estrogen receptors, progesterone receptors, interleukin-1 receptor. Published paragraphs 0023-0026 include enzyme targets such as endothelial nitric oxide synthase, cathepsin H, cathepsin S, etc. The estrogen receptor is not disclosed to be an enzyme, nor is it generally known in the art to be classified as such.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-15, 19, 20 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to a method of generating an optical image of an animate subject, said image being useful in the diagnosis of endometriosis..., wherein said contrast agent is of formula I, V-L-R (I) wherein V is an organic drug-like small molecule having affinity for the estrogen receptor. The recitation that V is an organic drug-like small molecule is ambiguous because it is unclear to what extent a small molecule should be "like" a drug to be considered sufficiently drug-like to be within the scope of the claims. The term drug-like is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. As such, the metes and bounds of the claims are not clearly set forth and the scope of the invention cannot be distinctly ascertained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 13, 19, 20 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fevig (*J. Med. Chem.*, 1987, 30, p.156-165), in view of Wallace (US 6,096,874) in further view of Poss (US 2005/0214221).

Fevig discloses thioether-linked norhexestrol-fluorophore conjugates as shown in Table III, having high estrogen receptor binding affinity and favorable fluorescence quantum yield. The compounds are intended for use in optical imaging of tumor, e.g. such as in breast cancer (see page 156, Table III, page 162).

Fevig does not specifically recite generating and optical image for diagnosis of endometriosis with the compounds, and does not teach flurophores having absorption maximum in the range of 600 to 1300 nm.

However, in addition to breast cancer, estrogen receptor-rich tissues may also be found in breast, ovarian, uterine and brain tissue.

For example, Wallace teaches tamoxifen derivatives having a tamoxifen derivative conjugated to a DTPA diagnostic moiety. The compounds are used as highly specific imaging agents for estrogen-receptor rich tissues (abstract). They may be used in imaging of estrogen receptors, for example in breast, ovarian, uterine and brain

tissues and may therefore be useful in the diagnosis of estrogen receptor positive cancers, meningiomas and endometriosis (column 1, lines 20-35). See also Example 26. ^{111}In-DTPA-TX can detect ER(+) breast tumors, it is useful to detect other ER(+) lesions (e.g. ovarian cancer, meningioma, endometriosis).

Poss teaches optical imaging probes and use of such probes for diagnosis and monitoring disease. The optical imaging probes can be used to identify and characterize normal and diseased tissues with regards to altered metabolic activity (abstract). Molecular optical imaging is a new imaging modality that generates molecular images using penetrating light rays. Preferably, light in the red and near infrared range (600-1200 nm) is used to maximize tissue penetration and minimize absorption from natural biological absorbers (paragraph 0007). There is a need for in vivo optical metabolite probes that are safer, less expensive and more convenient than current nuclear imaging probes (paragraph 0011). Optical imaging probes are disclosed having the formula $M(_n)$-F, where M is a metabolically recognizable molecule and F is a fluorochrome. Fluorochromes includes NIRFs having absorption and emission maximum between 600 and 1200 nm (paragraph 0021). Metabolically recognizable molecules include estrogen; estradiol (paragraph 0023, 0026). In vivo methods for optical imaging are also disclosed, including (a) administering to a subject an optical imaging probe (b) allowing time for the optical imaging probe to reach the target tissue and, preferably, but not necessary, for molecules in the target tissue to metabolize the probe; (c) illuminating the target tissue with light of a wavelength absorbable by the optical imaging probe; and (d) detecting the optical signal emitted by

the optical imaging probe (paragraph 0032). The methods can be used in the detection, characterization and/or determination of the localization of a disease, especially early disease (paragraph 0038). Exemplary fluorochromes include Cy5.5, Cy5, Cy7, AlexaFluor, indocyanine green, etc (paragraph 0072).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide compounds of Fevig for diagnosis of additional ER(+) lesions in addition to breast tumor, such as endometriosis, when the disclosure of Fevig is taken in view of Wallace. Both Fevig and Wallace are directed to diagnostic imaging of tumor or cancer using diagnostic moieties conjugated to targeting agents directed to estrogen receptor. Since Wallace teaches compounds having affinity for estrogen receptor may be useful for imaging estrogen receptors and may therefore be useful in the diagnosis of endometriosis, one would have had a reasonable expectation of success in using Fevig's compounds having high affinity for estrogen receptor for use in diagnosing endometriosis. It would have been further obvious to substitute one functionally equivalent optical imaging moiety for another in the compounds of Fevig, such as those disclosed by Poss. One would have been motivated to do so because Poss teaches that targeted fluorophores having and emission wavelengths in the near infrared spectrum are preferred, i.e., 600-1200 nm have benefits such as (1) high quantum yield, (2) narrow excitation/emission, (3) high chemical and photostability, etc., (paragraph 0021), and also teaches estrogen/estradiol as metabolically recognizable molecules.

Claims 13, 19, 20 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rahul ("Detection of Estrogen Receptor Status on Breast Cells Using Estradiol-Fluorescent Dye Conjugate," 2003-03-07, Indian Institute of Technology, thesis abstract) in view of Wallace (US 6,096,874).

Rahul teaches that the specificity of molecular marking and advantages of Optical Imaging has provided motivation to propose a novel technique for breast cancer diagnosis. Breast cancer cells express the receptors for estrogen and progesterone on their surfaces. These receptors can be used as a target for the delivery of fluorescent-tagged molecules. The importance of detecting these receptors lies not only in the field of diagnosis but also in determining the therapy and prognosis for the patients and in turn helps us in achieving individualized patient care. The use of estrogen dye conjugates consisting of a fluorescent cyanine dye (hydrophilic derivatives of Indocyanine Green) and estradiol was proposed for the detection of estrogen receptors on breast cancer cells. This report discusses the synthesis and characterization of novel hydrophilic cyanine dyes:bis-1,1-(4-sulfobutyl) indotricarbocyanine-5,5-dicarboxilic acid and bis-1,1-(4-sulfobutyl) indotricarbocyanine-5-carboxilic acid. These dyes have been tagged on to estradiol and the conjugate has been successfully charaterized. This technique may offer potential of non-invasive detection of the hormone receptor status in vivo and may help in decreasing the load of unnecessary biopsies, made only on the basis of positive mammography results in cases of breast carcinoma.

Rahul does not specifically recite generating and optical image for diagnosis of endometriosis with the compounds.

However, in addition to breast cancer, estrogen receptor-rich tissues may also be found in breast, ovarian, uterine and brain tissue.

For example, Wallace teaches tamoxifen derivatives having a tamoxifen derivative conjugated to a DTPA diagnostic moiety. The compounds are used as highly specific imaging agents for estrogen-receptor rich tissues (abstract). They may be used in imaging of estrogen receptors, for example in breast, ovarian, uterine and brain tissues and may therefore be useful in the diagnosis of estrogen receptor positive cancers, meningiomas and endometriosis (column 1, lines 20-35). See also Example 26. ^{111}In-DTPA-TX can detect ER(+) breast tumors, it is useful to detect other ER(+) lesions (e.g. ovarian cancer, meningioma, endometriosis).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide compounds of Rahul for diagnosis of additional ER(+) lesions in addition to breast tumor, such as endometriosis, when the disclosure of Rahul is taken in view of Wallace. Both Rahul and Wallace are directed to diagnostic imaging of tumor or cancer using diagnostic moieties conjugated to targeting agents directed to estrogen receptor. Since Wallace teaches compounds having affinity for estrogen receptor may be useful for imaging estrogen receptors and may therefore be useful in the diagnosis of endometriosis, one would have had a reasonable expectation of success in using Rahul's compounds having high affinity for estrogen receptor for use in diagnosing endometriosis.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is (571)272-9928. The examiner can normally be reached on Monday-Tuesday and Thursday-Friday 9 AM-5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

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